UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/359,672	07/23/1999	CATHERINE CLARE BUCKBURN	06854/0005501	3103

7590 02/12/2003

FINNEGAN HENDERSON FARABOW GARRETT &
DUNNER LLP
1300 I STREET NW
WASHINGTON, DC 200053315

EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
2656	25

DATE MAILED: 02/12/2003

Please find below and or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/359,672	BLACKBURN ET AL.
Examiner	**Art Unit**
Quang Nguyen, Ph.D	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-40,42,43,47-50 and 55-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-40,42,43, 47-50 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☒ Interview Summary (PTO-413) Paper No(s). 23
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Applicants' amendment filed on 12/04/02 in Paper No. 21 has been entered.

Amended claims 33-40, 42-43, 47-50 and newly added claims 55-58 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Following is a new ground of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-40, 42-43, 49-50 and 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 and its dependent claims, and claim 58 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is the step of assaying the biological effect of presence of a protein or polypepeptide or other product of DNA expression in the recited mouse cell. As written, the phrase "maintaining the isolated mouse cells over a plurality of generations so as to assay" does not constitute a positive action step for actually assaying. Maintaining the

isolated mouse cells over a plurality of generations is not an assaying step. Therefore, the end result of the method does not match with the preamble of the claimed method.

In claim 35, the phrase "transfecting the mouse cell of step (b)" on lines 5-6 of the claim is unclear. Is the step of transfection with a third vector before or after the transfection with the second vector? Does the transfected mouse cell of step (b) even contain the second vector? It appears that Applicants intend to transfect the mouse cell of step (c) with the third vector.

In claim 36, the phrase "assaying the effect of expression of each of the cDNAs" on lines 1-2 of the claim does not contain any active step of assaying. Additionally, claim 36 recites the limitation "each of the cDNAs according to the method of claim 33" on line 2. There is insufficient antecedent basis for this limitation in the claim. This is because there is no recitation of any cDNAs in claim 33, and there is no explicit linkage between the second vector of claim 33 with the cDNAs recited in claim 36.

In claim 37 and its dependent claims, as written it is unclear what is encompassed by the phrase "expressing ..... in a mouse cell" in step (a). Does the phrase "in a mouse cell" refer to cell used in the method or to the cell from which the DNA coding for the cell active protein is derived? Examiner suggests the phrase - - (a) expressing in a mouse cell selected from the group consisting of an ES cell, an EC cell, an EG cell, and differentiated progeny thereof, a composite DNA....." for overcoming this rejection.

Claim Rejections - 35 USC § 102

Amended claims 33-35 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Gassmann et al. (Proc. Natl. Acad. Sci. 92:1292-1296, 1995, IDS).

Gassmann et al. disclose as an exemplification the preparation of mouse ES clone 1.19 cells that contain episomal pMGD20neo DNA and express the polyoma large T antigen. These clonal cells further support the replication, episomal maintenance and expression of hygromycin B under the control of the phosphoglycerate kinase promoter of a second plasmid PGKhphΔLT20. The second plasmid also contains the polyoma *ori*, and a large T gene with a 1249-bp deletion in the coding sequence (page 1295, column 1, see entire first paragraph). For further details on the disclosed pMGD20neo and PGKhphΔLT20 vector plasmids, please refer to Fig. 1. Gassmann et al. teach that the yield of hygromycin B-resistant clones was about 100 times greater with PGKhphΔLT20 than with the control plasmid PGKhph that lacks the polyoma segment (page 1295, col. 1, first full paragraph). This has been attributed to the ability of the PGKhphΔLT20 DNA to replicate from its own ori in the presence of large T provided by the already established episomal pMGD20neo DNA. Gassmann et al. specifically teach that plasmid(s) containing a polyoma ori, a selectable marker and any other gene(s) of interest could be established and maintained in transfected cells with preexisted or established presence of polyoma large T, e.g., mouse ES clone 1.19 cells that contain episomal pMGD20neo plasmid, and that the capability to establish plasmids as episomes in ES cells should find utility for a variety of studies of gene regulation in these cells; e.g., gene expression, molecular complementation, DNA replication and recombination and genetic control of differentiation in ES cells and during murine

embryogenesis (page 1296, col. 1, bottom of the second full paragraph and top paragraph of col. 2).

Therefore, the teachings of Gassmann et al. meet the limitation of these claims, and thus the reference anticipates the instant claims.

Response to Applicants' comments

Applicants' comments related to the above rejection in the Amendment filed on 12/04/02 in Paper No. 21 (page 13) have been fully considered.

Applicants draw the Examiner to a paper by Camenisch et al., which names Gassmann as a co-author. Applicants believe that the reference of Gassmann et al. can not be read in isolation because the later paper by Camenisch et al. provides an insight into the direction taken by Gassmann et al. following their initial work on maintenance of extrachromosomal plasmid vectors in mouse embryonic stem cells, which is to use a single vector system for expression of genes of interest.

Applicants' comments are respectfully found to be irrelevant to the above rejection, because the teachings of Gassmann et al. clearly anticipate the instant claims. With respect to the paper of Camenish et al., there is no teachings stating or suggesting that the episomal vector system taught by Gassmann et al. would not work, and that the single vector system for expression of genes of interest disclosed in the paper of Carmenish et al. is simply a variant of Gassmann et al.'s previous teachings.

Claim Rejections - 35 USC § 103

Amended claims 33, 36, 56 and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gassmann et al. (Proc. Natl. Acad. Sci. 92:1292-1296, 1995, IDS) in view of Cooper et al. (U.S. Patent No. 5,770,374 with an effective filing date at least to 11/12/1993) and Carstens et al. (Gene 164:195-202, 1995, Cited previously).

With respect to the enabled scope of the present invention, Gassmann et al. disclose as an exemplification the preparation of mouse ES clone 1.19 cells that contain episomal pMGD20neo DNA and express the polyoma large T antigen. These clonal cells further support the replication, episomal maintenance and expression of hygromycin B under the control of the phosphoglycerate kinase promoter of a second plasmid PGKhphΔLT20. The second plasmid also contains the polyoma *ori*, and a large T gene with a 1249-bp deletion in the coding sequence (page 1295, column 1, see entire first paragraph). For further details on the disclosed pMGD20neo and PGKhphΔLT20 vector plasmids, please refer to Fig. 1. Gassmann et al. teach that the yield of hygromycin B-resistant clones was about 100 times greater with PGKhphΔLT20 than with the control plasmid PGKhph that lacks the polyoma segment (page 1295, col. 1, first full paragraph). This has been attributed to the ability of the PGKhphΔLT20 DNA to replicate from its own ori in the presence of large T provided by the already established episomal pMGD20neo DNA. Gassmann et al. specifically teach that plasmid(s) containing a polyoma ori, a selectable marker and any other gene(s) of interest could be established and maintained in transfected cells with preexisted or established presence of polyoma large T, e.g., mouse ES clone 1.19 cells that contain episomal pMGD20neo plasmid, and that the capability to establish plasmids as

episomes in ES cells should find utility for a variety of studies of gene regulation in these cells; e.g., gene expression, molecular complementation, DNA replication and recombination and genetic control of differentiation in ES cells and during murine embryogenesis (page 1296, col. 1, bottom of the second full paragraph and top paragraph of col. 2).

Gassmann et al. do not specifically teach the *in vitro* assay of claim 33, wherein the second vector contains a DNA that codes for an antisense RNA or wherein further comprising the step of isolating the DNA coding for the protein or polypeptide or other product of DNA expression. Nor do Gassmann et al. teach a method of screening a library of cDNAs using the method of claim 33.

However, at the effective filing date of the present application, Cooper et al. already teach that Epstein-Barr virus (EBV)-based episomes have been used to efficiently screen cDNA libraries (col. 1, lines 58-62). Cooper et al. also teach an episomal vector system for expressing a foreign gene in a mammalian cell as well as for cDNA library cloning (see Summary of the Invention). Specifically, Cooper et al. teach that their episomal vector system can be used to identify potentially novel dominant oncogenes and/or antioncogenes that are involved in tumor progression by both sense and anti-sense cDNA library screening (col. 17, lines 9-33).

Carstens et al. also disclose an EBV-based episomal vector system that allows functional cloning of regulatory genes by expression of libraries of cDNA inserts either in the sense or antisense direction (see abstract). Carstens et al. further teach that generally, although it is sufficient to place EboriP and the EBNA-1 (viral replication

factor) gene on the same vector and vectors harboring both elements have been successfully used to clone genes from expression libraries in human cells, vector/host systems expressing EBNA-1 **in trans** have been reported to be **more efficient** in generating stable, transfected colonies of human cells than systems in which EBNA-1 is only provided by the vector (page 196, col. 2, under the section "Construction and properties of CMV-EL and C1E-EL").

Accordingly, it would have been obvious and within the level of skill for an ordinary artisan to adapt the episomal plasmid vector system taught by Gassmann et al. for screening both sense and antisense cDNA libraries for genes involved in the differentiation of mouse ES cells and/or during murine embryogenesis in light of the teachings of Cooper et al. and Carstens et al. It would also have been obvious for an ordinary skilled artisan to divide mouse ES cells harbouring a first episomal vector expressing polyoma large T antigen into two distinct cell populations for subsequent transfections with two distinct episomal vectors coding for different gene products to assay for their biological effects.

One of ordinary skilled in the art would have been motivated to carry out the above modification because the episomal vector system taught by Gassmann et al. provides the viral replication factor *in trans*, which has been reported to be efficient in generating stable transfected cells as well as it allows the utilization of rodent cells in the screening of cDNA libraries because of the inherent limitation of the EBV-based shuttle vector system (applicable for most mammalian cells with the exception of rodent cells; see Carstens et al., page 196, col. 2, top of the second paragraph). Moreover,

one of ordinary skilled artisan would have a reasonable expectation of success because Gassmann et al. have demonstrated successfully by exemplification that mouse ES cells containing episomal pMGD20neo DNA and expressing the polyoma large T antigen (supplied in *trans*) support an efficient replication, episomal maintenance and expression of hygromycin B of a second plasmid PGKhphΔLT20 containing the polyoma *ori*.

Therefore, the claimed invention was *prima facie* obvious in the absence of evidence to the contrary.

Response to Applicants' argument

Applicants' arguments related to the above rejection in the Amendment filed on 12/04/02 in Paper No. 21 (pages 10-12) have been fully considered.

Applicants argue mainly that Carstens et al. explicitly teach that their shuttle vector-based systems do not operate on rodent cells, and therefore Carstens et al. does not provide a teaching that is relevant to expression in mouse cells. Additionally, Gassmann et al. relate to plasmid vectors in mouse embryonic stem cells, and that one of skill in the art would not be motivated to combine the teachings of Gassman et al. and Carstens et al.

Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, Gassmann et al. clearly teach an episomal vector system that is functional in mouse cells, specifically mouse ES cells. Additionally, Gassmann et al.

teach that plasmid(s) containing a polyoma ori, a selectable marker and any other gene(s) of interest could be established and maintained in mouse ES cells expressing large T antigen provided by an already established episomal vector. Gassmann et al. further teach that the episomal vector system has utility for a variety of studies of gene regulation in mouse ES cells; e.g., gene expression, molecular complementation, DNA replication and recombination and genetic control of differentiation in ES cells and during murine embryogenesis (page 1296, col. 1, bottom of the second full paragraph and top paragraph of col. 2).

Secondly, at the effective filing date of the present application Epstein-Barr virus (EBV)-based episomes, an episomal vector system, have been used to efficiently screen cDNA libraries as evidenced by the teachings of Cooper et al. and Carstens et al. Therefore, it would have been obvious and within the level of skill for an ordinary artisan to adapt the episomal plasmid vector system taught by Gassmann et al. for screening cDNA libraries for genes involved in the differentiation of mouse ES cells and/or during murine embryogenesis in light of the teachings of Cooper et al. and Carstens et al. One of ordinary skilled in the art would have been motivated to carry out the above modification because the episomal vector system taught by Gassmann et al. provides the viral replication factor *in trans*, which has been reported to be efficient in generating stable transfected cells as well as it allows the utilization of rodent cells in the screening of cDNA libraries because of the inherent limitation of the EBV-based shuttle vector system (applicable for most mammalian cells with the exception of rodent cells; see Carstens et al., page 196, col. 2, top of the second paragraph).

Accordingly, amended claims 33, 36, 56 and 57-58 are rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Amended claims 37-40, 42-43 and 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gassmann et al. (Proc. Natl. Acad. Sci. 92:1292-1296, 1995, IDS) in view of Cooper et al. (U.S. Patent No. 5,770,374 with an effective filing date at least to 11/12/1993) and Carstens et al. (Gene 164:195-202, 1995, Cited previously) as applied to claims 33, 36, 56 and 57-58 above, and further in view of Lok (U.S. Patent No. 5,753,462), Williams et al. (Nature 336:684-687, 1988; Cited previously), Moreau et al. (Nature 336:690-692, 1988; Cited previously) and Nichols et al. (Exp. Cell Res. 215:237-239, 1994).

The combined teachings of Gassmann et al., Cooper et al. and Carstens et al. have been discussed and applied as above. However, none of the references specifically teaches an *in vitro* method for assaying or screening for a DNA codes for a polypeptide that directs transport of a cell active protein to a cell surface, wherein the cell active protein inhibits differentiation of the cell and in the absence of the cell active protein the cell will differentiate.

At the effective filing date of the present application, Lok already teaches a method for trapping signal sequences as a strategy for cloning cDNA of unidentified secreted and transmembrane proteins, particularly those involved in signal transduction (see abstract). Lok teaches that the expression vectors comprising the following operably linked elements: a transcription promoter; a first DNA segment encoding a

cloning site for insertion of a 5' terminal DNA fragment: a second DNA segment encoding a leader-less protein, whereby in-frame joining of the second DNA segment with the first DNA segment provides cell surface expression of the leader-less protein if a functional signal sequence is inserted in the cloning site; and a transcription terminator (col. 2, lines 11-19). Lok further teaches the various approaches available for detection/selection of signal sequence cDNAs, including a biological selection procedure exemplified by a prototype in which the leader-less protein encoded by the expression vector is a cytokine receptor (including IL-6 receptor) or a growth factor receptor, and when such receptor is introduced into a factor-dependent cell line, cell surface expression of the receptor permits cell proliferation (i) in the presence of the receptor's corresponding cytokine or growth factor, and (ii) in the absence of the factor(s) upon which the starting cell-line is dependent (see cols. 8-9). Additionally, Lok teaches that such biological selection protocol is an attractive alternative to automated cell sorting/selection since it does not require an expensive specialized piece of equipment and can be conveniently performed in most laboratory settings (col. 11, lines 28-33).

Also at the effective filing date of the present application, Williams et al. already teach that in the presence of a secreted leukemia inhibitory factor (LIF), mouse ES cells retain the stem cell phenotype of compact colonies of small cells with a large nuclear to cytoplasmic ratio *in vitro*, whereas ES cells maintained in normal culture medium without LIF differentiate into colonies containing large, flat differentiated cells over a period of 3-6 days (page 684, column 2, last paragraph continues to top of column 1,

page 685). Moreau et al. already disclose the complete cDNA sequence for a secreted LIF (Fig. 1). Nichols et al. also teach that mouse ES cells do not express IL-6 specific receptor component, and are therefore unresponsive to IL-6 alone. However, in the presence of a complex of IL-6/sIL-6R mouse ES cell lines can be maintained *in vitro* in an undifferentiated state similar to those in the presence of LIF (see page 237 in the Introduction). This result also suggests that mouse ES cells expressing exogenous functional IL-6 receptors in the presence of IL-6 can retain the stem cell phenotype *in vitro*.

Accordingly, it would have been obvious and within the skill level of an ordinary artisan to modify the episomal vector system taught by Gassmann et al. for cloning or screening DNAs coding for unidentified secreted proteins and membrane proteins based on the signal sequence trap approach by expressing a composite DNA in a polyoma virus-based shuttle vector system in mouse ES cells, in which a DNA coding for a leaderless leukemia inhibitory factor (LIF or IL-6) or a leaderless IL-6 receptor is used to trap NH2-terminal signal encoded sequences, and select for cells containing DNA coding for signal sequences under suitable conditions based on the differentiation state of mouse ES cells in culture, in light of the combined teachings of Cooper et al., Carstens et al., Lok, Williams et al., Moreau et al. and Nichols et al. It would have been obvious for an ordinary skilled artisan to select biological conditions known in the art regarding to the differentiation state of ES cells in culture to select for mouse ES cells containing DNA coding for signal sequences because of the distinct phenotypes exhibited between differentiated or non-differentiated ES cells in culture, and that when

an ordinary skilled artisan utilizes ES cells in any studies, the differentiation state of the utilized ES cells is always an issue that is addressed. For example, in disclosing the maintenance of an extrachromosomal plasmid vector system in mouse embryonic stem cells, Gassmann et al. concern about whether the expression of polyoma large T would affect the ES cell's totipotency, but also suggest studies for investigating molecular mechanisms in differentiating ES cells (see last paragraph on col. 1 of page 1296 continues to col. 2).

One of ordinary skill in the art would have been motivated to carry out the above modification because the polyoma virus-based shuttle vector system in mouse ES cells taught by Gassmann et al. offers various advantages as already noted by Carstens et al. for a similar Epstein-Barr virus based shuttle vector system. These advantages include a) easy recovery of the library vectors from selected clones, (b) expression level of the cDNA expression cassette is unaffected by integration, and (c) no cDNA expression cassettes are lost due to disruption of the vector following integration into genomic DNA (see Carstens et al., page 196, column 1, last paragraph continues to the top of column 2). Moreover, unlike the Epstein-Barr virus based shuttle vector system, the polyoma virus-based shuttle vector system of Gassmann et al. is applicable to both mammalian cells and rodent cells (e.g., mouse ES cells) as well as its capability to provide the viral replication factor *in trans*, which has been reported to be efficient in generating stable transfected cells. Furthermore, one of ordinary skilled artisan would have been motivated to carry out the above modification because it would allow an easy biological selection procedure for identification of a mouse ES cell containing a DNA

sequence coding for a signal polypeptide on the basis of its induced morphological or proliferative change due to the presence or absence of a secreted LIF or in the presence of absence of a functional IL-6 receptor.

Thus, the claimed invention was *prima facie* obvious in the absence of evident to the contrary.

Following are new grounds of rejections necessitated by Applicants' amendment.

New Matter

Amended claims 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 47 recites "otherwise obtaining a transgenic mouse cell, selected from the group consisting of an ES cell, an EC cell and an EG cell, that expresses the replication factor", and claim 48 is dependent upon claim 47. There is literally no support in the originally filed specification (including page 7 of the specification as pointed to by Applicants in the Amendment) for Applicants' contemplation of using the selected transgenic mouse cell expressing the replication factor (obtained from a transgenic mouse) in the methods as claimed. While the specification teaches in general for transfecting a mouse ES cell, a mouse EC cell and a mouse EG cell with a vector that expresses a viral replication factor, there is no teachings or literal support for obtaining a mouse ES cell, a mouse EC cell or a mouse

EG cell expressing a viral replication factor from any transgenic mouse, then using it in the claimed methods. Therefore, given the lack of written support on this aforementioned issue from the originally filed specification, it would appear that Applicants did not have possession of the claimed invention at the time the application was filed.

Written Description

Amended claims 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. "Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

An embodiment of Applicant's invention is drawn to an *in vitro* method of assaying whether a DNA under investigation codes for a polypeptide that directs transport of a cell active protein to a cell surface utilizing a transgenic mouse cell selected from the group consisting of an ES cell, an EC cell and an EG cell that

expresses a viral replication factor. The instant specification fails to disclose the making of any transgenic mouse from which an ES cell, an EC cell and an EG cell expressing an effective level of a viral replication factor that is capable of supporting an episomal replication of a second vector in the methods as claimed. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of any transgenic mouse from which an ES cell, an EC cell and an EG cell expressing an effective level of a viral transcriptional factor essential for the extrachromosomal replication of the second vector to be utilized in the methods as claimed. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

Amended claims 33, 55 and 37-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(a) The *in vitro* assay of claim 33, wherein the viral replication factor is a viral replication factor selected from polyoma large T antigen, papilloma virus replication factors, and SV40 large T antigen;

(b) The *in vitro* method of claim 37, wherein the mouse cell is selected from the group consisting of an ES cell, an EC cell and an EG cell; and wherein the composite DNA is expressed by transfecting the mouse cell with a first vector that expresses a viral replication factor;

does not reasonably provide enablement for the *in vitro* assay wherein the viral replication factor is EBNA-1 antigen, and the *in vitro* method of assaying utilizing differentiated progeny of a mouse ES cell, a mouse EC cell or a mouse EG cell, or for utilizing a transgenic mouse cell selected from the group consisting of an ES cell, an EC cell and an EG cell, that expresses a viral replication factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification is not enabled for the instant broadly claimed invention for the following reasons.

(a) The breadth of the claims. Claims 33 and 55 encompass an *in vitro* assay specifically utilizing an expressed EBNA-1 antigen to support the replication of a second vector in a mouse ES cell, a mouse EC cell or a mouse EG cell or a differentiated derivative thereof. Claims 37-50 encompass an *in vitro* method of assaying whether a DNA under investigation codes for a polypeptide that directs transport of a cell active protein to a cell surface utilizing differentiated progeny of a mouse ES cell, a mouse EC cell or a mouse EG cell to express a composite DNA, wherein said method further comprises the step of determining if the cell differentiates. An embodiment of claims 47-48 encompasses the utilization of a selected transgenic mouse cell expressing a viral replication factor to support the replication of a second vector in the method as claimed.

(b) The state of the prior art and the unpredictability of the art. With respect to claims 33 and 55, at the effective filing date of the present application it is already well known in the art that the Epstein-Barr virus (EBV)-based episomal vector

system is applicable in most mammalian cells with the exception of rodent cells (Carstens et al., Gene 164:195-202, 1995; Cited previously, page 196, col. 2, top of second paragraph). With respect to claims 47-48, the art of transgenesis was known to be highly unpredictable with respect to the unpredictability of the incorporation and expression of a transgene to a desired expression level in any animal species. The individual transgene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a desired phenotype (for this instance, a transgenic mouse expresses a viral replication factor in its ES, EG and EC cells at a level to support the episomal replication of a second vector). This observation is supported by Wall (Theriogenology 45:57-68, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (page 61, last paragraph).

(c) The amount of direction or guidance provided. Apart from the exemplification showing the utilization of a polyoma-based episomal vector system in a mouse ES cell, the instant specification fails to provide any guidance for a skilled in the art how to make and use an Epstein-Barr virus (EBV)-based episomal vector system in an *in vitro* assay using a mouse ES cell, a mouse EG cell, a mouse EC cell or a differentiated progeny thereof as claimed. As noted previously that the EBV-based episomal vector system is known to be applicable in most mammalian cells with the exception of rodent cells. Therefore, given the lack of any guidance provided by the

present disclosure on this matter, it would have required undue experimentation for a skilled artisan to make and use the full scope of the assay as claimed.

The instant specification also fails to provide any specific guidance on the making of any transgenic mouse from which an ES cell, an EC cell and an EG cell expressing an effective level of a viral replication factor that is capable of supporting an episomal replication of a second vector in the methods as claimed. With the lack of sufficient guidance provided by the present disclosure, coupled with the unpredictability of the incorporation and expression of a transgene to a desired expression level in any animal species known in the transgenic art, it would have required undue experimentation for a skilled artisan to make and use the full scope of the method as claimed.

With respect to an embodiment of claims 37-50, it is unclear how one can determine if a cell differentiates or not in the *in vitro* assay as claimed, when differentiated progeny of a mouse ES cell, a mouse EG cell or a mouse EC cell is a starting material. The instant specification fails to provide any guidance for a skilled artisan on how to make and use such an assay, and therefore it would have required undue experimentation for a skilled artisan to practice the assay method as claimed.

Accordingly, due to the lack of sufficient guidance provided by the instant specification regarding to the issues set forth above, and the breadth of the claims, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

Gerald G. Leffers Jr
PATENT EXAMINER
Gerald G. Leffers Jr
A.U. 1636